

09/743288

423 PCT/PCT 06 JAN 2001

METHOD
FOR SEPARATING
HYDROXYMETHYLTHIOBUTYRIC ACID

Frédéric Carencotte
Michel Garrait

-and-

Georges Gros

TRANSLATION OF
(FRENCH)
INTERNATIONAL APPLICATION

PCT/FR99/01636 IFD: 07/07/1999

-with-

One (1) Sheet of Drawing

ST-98/020 (5500*59)

"Express Mail" mailing label
number EE617838735

Date of Deposit
January 08, 2001

I hereby certify that this paper or fee is
being deposited with the United States Postal
Service "Express Mail Post Office to
Addressee" service under 37CFR 1.10 on the
date indicated above and is addressed to BOX
PCT, Commissioner for Patents,
Washington, D.C. 20231.

Barbara J. Miller
(Typed or printed name of person mailing
paper or fee)

Barbara J. Miller
(Signature of person mailing paper or fee)

WO 00/02853

1

PCT/FR99/01636

534 Rec'd PCT/PTO 08 JAN 2001

PROCESS FOR THE SEPARATION OF HYDROXYMETHYLTHIOBUTYRICACID

The present invention relates to an improved
5 process for the preparation of 2-hydroxy-4-methylthio-
butyric acid (HMTBA) in the form of an aqueous solution
and more especially to a process for improved
separation from a 2-hydroxy-4-methylthiobutyronitrile
(HMTBN) acid hydrolysate mixture. 2-Hydroxy-4-
10 methylthiobutyric acid, an analog of l-methionine, is
used in animal nutrition.

Cummins discloses, in Patent US 3 773 927, a
process in which HMTBA is produced by hydrolysis of
HMTBN with hydrochloric acid under conditions such that
15 the suspension produced comprises solid ammonium
chloride, which is removed by centrifuging. The
filtrate is subsequently vacuum distilled to remove the
water. This Patent US 3 773 927 discloses a process for
the preparation of an aqueous liquid product with a
20 high concentration of HMTBA acid (85 to 90% by mass).
This type of product, obtained by such a process, has a
strong smell and a dark color and comprises ester
oligomers. These characteristics are probably due to
the high temperature conditions applied to a product
25 with a low water content during the final dehydration
stage. The other disadvantages of this process are a
high energy consumption during the same stage and

difficulties and losses in yields during the centrifuging or the filtration.

Patent US 2 745 745 discloses the separation of HMTBA by extraction with a water-immiscible organic phase, such as diethyl ether. British Patent No. 915 193 discloses a process for the preparation of calcium salts of HMTBA where the latter is extracted with an ether, such as isopropyl ether or butyl ether, having a boiling point greater than that of ethyl ether. Water is added to form an emulsion, to which calcium carbonate or calcium hydroxide is added to precipitate the calcium salt of HMTBA. This patent does not relate to the preparation of liquid products comprising essentially HMTBA.

Gielkens mentions, in Patent US 3 175 000, that the direct extraction of HMTBA from the hydrolysate gives poor yields. In this patent, the extraction is only used as a secondary recovery means.

Patent US 4 524 077 discloses the liquid-liquid extraction of HMTBA by a water-immiscible organic solvent, preferably methyl isobutyl ketone, and then the recovery of the HMTBA from the extract obtained comprising a minimum of 5% by weight of water on the basis of the mass of HMTBA recovered. The product thus prepared has a lighter color, less of a smell, a lower viscosity and a better thermal stability.

than the products prepared by the conventional processes described above.

Patent EP 0 330 527 discloses a process for the separation of HMTBA which consists in forming two phases by addition of aqueous ammonia to the hydrolysis solution, each of the phases, the first organic phase comprising the HMTBA and the second aqueous phase comprising the ammonium salt, are subsequently subjected to an evaporation operation, so as to remove the water. The concentrated filtered organic phase is subsequently diluted, so as to adjust its concentration to that of the commercial solution. The ammonium sulfate obtained from the aqueous phase is contaminated by sulfur residues, it often exhibits an unpleasant smell which makes it difficult to sell or which requires additional treatments in order to remove the smell therefrom. The present process requires a large amount of energy during the evaporation of the water from each of the phases obtained after neutralization and an additional treatment stage for the ammonium sulfate, which is also expensive. The present invention has made it possible to solve the abovementioned problems.

Description of the invention

The present invention relates to a novel process for the preparation of 2-hydroxy-4-

methylthiobutyric acid (HMTBA) and more specifically to
a novel process for the separation of HMTBA. This
process consists, in a first stage, in adding a
neutralizing agent, composed of ammonium hydroxide, to
5 the solution from the hydrolysis with sulfuric acid of
2-hydroxy-4-methylthiobutyronitrile, which results in
the separation of the medium into two phases. These two
phases are composed of an organic phase, which is
subjected to a stage of release of the salts by
10 addition of an organic solvent, and of an aqueous
phase, from which residual 2-hydroxy-4-methylthio-
butyric acid is exhaustively extracted by addition of
an organic solvent.

The system for release of the salts from the
15 organic phase is composed of the addition of a solvent
which is not very miscible with water. Mention may be
made, among these solvents, of any solvent, chemically
compatible with the medium and exhibiting little
affinity for water, which makes it possible to dissolve
20 the HMTBA. They can be chosen from ketones, aldehydes,
ethers, esters, carbonates or alcohols. They are
preferably ketones of low molecular weight, such as
methyl ethyl ketone or methyl isobutyl ketone (MIBK),
or ethers, such as methyl tert-butyl ether or
25 diisopropyl ether, or carbonates, such as diethyl

carbonate. They are more preferably methyl ethyl ketone, methyl isobutyl ketone and ethyl carbonate.

The system for exhaustively extracting the HMTBA from the aqueous phase is composed of the
5 addition of a solvent which is not very miscible with water. Mention may be made, among these solvents, of any solvent, chemically compatible with the medium and exhibiting little affinity for water, which makes it possible to dissolve the HMTBA. They can be chosen from
10 ketones, aldehydes, ethers, esters, carbonates or alcohols. They are preferably ketones of low molecular weight, such as methyl ethyl ketone or methyl isobutyl ketone (MIBK), or ethers, such as methyl tert-butyl ether or diisopropyl ether, or carbonates, such as
15 diethyl carbonate. They are more preferably methyl ethyl ketone, methyl isobutyl ketone and ethyl carbonate.

Each of the stages, release of the salts from the organic phase and exhaustive extraction of the
20 aqueous phase, can be carried out independently of one another or can be carried out jointly during the implementation of the process for the isolation of the HMTBA. It is preferable to carry out these two stages jointly and in a continuous process.

25 In the case where it is desired to release the salts from the organic solution of HMTBA, the

amount of organic solvent which is added to the organic medium composed of HMTBA is according to a solvent/organic solution of HMTBA ratio by weight preferably of greater than 0.3 and more preferably 5 still of between 0.3 and 1. It is obvious that a person skilled in the art will adjust the amount of solvent to be used to the structure of the process. The temperature at which the release is carried out is compatible with the nature of the solvent used and in 10 particular lies below its boiling point.

In the case where it is desired to exhaustively extract the HMTBA from the aqueous solution, it is preferable, according to a better way of implementing the invention, to use an amount of 15 organic solvent with respect to the aqueous solution comprising the inorganic salts, in particular ammonium sulfate, drawn up according to an amount by weight of greater than 0.05 and preferably of between 0.1 and 0.5. The temperature at which the exhaustive extraction 20 is carried out is compatible with the nature of the solvent used and in particular lies below its boiling point.

The following stage consists in evaporating the organic solvent(s) used, which can be alike in the 25 two stages or different. This operation requires less

energy than the operation for the removal of water carried out in the prior art.

After evaporation of the solvent or solvents, which are optionally recycled for a fresh operation, an 5 organic phase is obtained which comprises little water and which comprises a greatly reduced amount of salts, which eliminates the filtration phase carried out previously. The phase is subsequently adjusted to the commercial assay of 88% by weight by addition of the 10 water needed.

After two-phase separation between the organic solvent for exhaustive extraction and the aqueous phase comprising the salts, a solution of salts and predominantly of ammonium sulfate is obtained, 15 which solution is crystallized and comprises virtually no more organic contaminants. The crystals are of better quality and exhibit virtually more smells. According to a first means of giving added value to these salts, these crystals are used in particular as 20 fertilizer or are intended for an industrial use.

According to a second means of giving added value to these salts, the aqueous solution of salts is treated by electrodialysis in order to regenerate, on the one hand, ammonia, which is optionally recycled to 25 the neutralization stage, and, on the other hand,

sulfuric acid, which, after concentration, is recycled to the stage of hydrolysis of the HMTBN.

According to a third means of giving added value to the salts, the solution of salts, which are 5 essentially composed of ammonium sulfate, is treated by the thermal route in a plant, for example a sulfuric regeneration plant, so as to recover concentrated sulfuric acid which can be recycled directly to hydrolysis of the HMTBN.

10 An industrial implementation of the combined process is carried out in the following way (cf. Figure 1).

The neutralized stream (stream 1) is separated by settling.

15 The organic phase resulting from the separation by settling is subjected to an operation of release of the salts by a treatment with a phase essentially composed of organic solvent (stream 6). This treatment consists of a liquid-liquid contact. It 20 is carried out in a conventional mixer-settler or in any other liquid-liquid contactor chosen from the following devices: a bank of mixer-settlers, a packed column, a perforated plate column, a rotating disk column, a centrifugal extractor, a pulsed column or any 25 other liquid-liquid contactor.

FICHES DE RECHERCHE

The extract and the raffinate are separated (stream 4 and stream 12). The raffinate is recycled to the stage of exhaustive extraction of HMTBA from the aqueous phase resulting from the separation by settling. The extract (stream 4) is subjected to a treatment targeted at removing the solvent. The removal is carried out in particular by evaporation, distillation or steam distillation. This removal operation is carried out in order to obtain an HMTBA at the bottom (stream 8) which is highly depleted in residual solvent and which is sufficiently concentrated, before an optional adjustment to the assay. The top stream (stream 5) originating from this removal of solvent is recycled

15 • partly to the stage of release with respect to the organic phase resulting from the separation by settling (stream 6)

 • partly to the stage of exhaustive extraction with respect to the aqueous phase resulting from the separation by settling (stream 7).

The aqueous phase which has been separated by settling (stream 10) is subjected to a treatment for exhaustive extraction of the HMTBA by contact with a phase essentially composed of organic solvent (stream 7). This treatment is also carried out in a liquid-liquid contactor, which can be a bank of mixer-

settlers, a packed column, a perforated plate column, a rotating disk column, a centrifugal extractor, a pulsed column or any other liquid-liquid contactor.

The extract and the raffinate are separated
5 (stream 11 and stream 13). The extract (stream 11) is recycled to the stage of release with respect to the organic phase resulting from the separation by settling, whereas the raffinate (stream 13) is subjected to a treatment targeted at removing the
10 solvent. This treatment is in particular a distillation, an evaporation or a stripping. It is preferably carried out during a crystallization of the ammonium sulfate by evaporation.

The present invention will be more fully
15 described with the help of the following examples, which must not be regarded as limiting the invention.

1 - Examples of liquid-liquid extraction which is carried out on the aqueous phase after separation by settling of the neutralized hydrolysis stream

20 The object of this operation is to extract the residual HMTBA present in the aqueous phase after separation by settling before crystallization of the ammonium sulfate.

The composition of the aqueous phase to be
25 extracted is as follows:

$$[\text{HMTBA}] = 3.7\% \text{ W/W}$$

[WATER] = 40.9% W/W

[salts] = 55.4% W/W

**Example of exhaustive extraction of this aqueous phase
with MIBK:**

5 505.9 grams of this aqueous phase stream were
brought into contact in a stirred 1 liter reactor with
56.2 grams of MIBK at a temperature of 75°C. The
extraction solvent/solution to be separated ratio was
11.1% W/W. After separation of the two phases by
10 settling at 75°C, the two phases were withdrawn and
analyzed:

The upper phase, in which the HMTBA is partially
extracted, represented 67.9 grams and had a load of
HMTBA of 20.5% W/W. The content of salts in this upper
15 phase was below the detection limit of the analytical
tool (potentiometry).

Thus, 74.3% of the participating HMTBA could
be extracted with MIBK in a single stage with a
participating organic solvent/solution to be extracted
20 ratio of 11.1%.

The lower phase, for its part, had a load of
HMTBA of 0.97% W/W.

The partition coefficient, expressed as
follows [HMTBA] upper phase/[HMTBA] lower phase, is
25 21.1.

2 - Example of exhaustive extraction of the aqueous phase with ethyl carbonate:

505.9 grams of the aqueous phase were brought into contact in a 1 liter stirred reactor with 56.2 5 grams of ethyl carbonate at a temperature of 75°C. The extraction solvent/solution to be separated ratio was 11.1% W/W. After separating the two phases by settling at 75°C, the two phases were withdrawn and analyzed: The upper phase, in which the HMTBA is partially 10 extracted, represented 67.3 grams and had a load of HMTBA of 14.2% W/W. The content of salts in this upper phase was below the detection limit of the analytical tool (potentiometry).

Thus, 50.3% of the participating HMTBA could 15 be extracted with ethyl carbonate in a single stage with a participating organic solvent/solution to be extracted ratio of 11.1%.

The lower phase, for its part, had a load of HMTBA of 1.53% W/W.

20 The partition coefficient, expressed as follows [HMTBA] upper phase/[HMTBA] lower phase, is 9.3.

3 - Example of exhaustive extraction of the aqueous phase with Methyl Ethyl Ketone

25 505.9 grams of aqueous phase were brought into contact in a stirred 1 liter reactor with

56.2 grams of MEK at a temperature of 75°C. The extraction solvent/solution to be separated ratio was 11.1% W/W. After separating the two phases by settling at 75°C, the two phases were withdrawn and analyzed:

5 The upper phase, in which the HMTBA is partially extracted, represented 65.3 grams and had a load of HMTBA of 23.7% W/W. The content of salts in this upper phase was below the detection limit of the analytical tool (potentiometry).

10 Thus, 82.9% of the participating HMTBA could be extracted with MEK in a single stage with a participating organic solvent/solution to be extracted ratio of 11.1%.

15 The lower phase, for its part, had a load of HMTBA of 0.6% W/W.

The partition coefficient, expressed as follows [HMTBA] upper phase/[HMTBA] lower phase, is 39.5.

**4 - Examples of liquid-liquid release carried out on
20 the organic phase after separation by settling of the
neutralized hydrolysis stream**

The object of this operation is to purify the organic phase from salts ($\text{NH}_4\text{}_2\text{SO}_4$ and NH_4HSO_4) by displacement of these salts into an aqueous phase which 25 is formed by addition of a solvent exhibiting little affinity for water.

The composition of the organic phase resulting from the separation by settling of the neutralized hydrolysis stream is as follows:

[HMTBA] = 66.6% W/W
5 [WATER] = 22.4% W/W
[salts] = 11% W/W

Example of extraction of the salts by addition of MIBK

379 grams of this organic phase stream were brought into contact in a 1 liter stirred reactor with 10 137.3 grams of MIBK at a temperature of 75°C. The extraction solvent/solution to be separated ratio was 36.2% W/W. After separation by settling at 75°C, the two phases formed were withdrawn and analyzed: The upper phase, in which the HMTBA was extracted, 15 represented 445.7 g and had a load of salts of 1%. Thus, with the participating organic solvent/solution to be treated ratio used, 89% of the salts present in the medium before extraction could be displaced into the aqueous phase created by the addition of MIBK.

20 The lower phase, into which the salts are partially displaced, represented 70.2 grams and had a load of HMTBA of 2% W/W. Thus, under these displacement conditions, 99.4% of the participating HMTBA could be extracted with MIBK in one stage with a participating 25 organic solvent/solution to be treated ratio of 36.2%.

The lower phase, for its part, had a load of salts of 53% W/W.

The partition coefficient, expressed as follows [salts] lower phase/[salts] upper phase, is 53.

5 5 - Example of extraction of the salts by addition of ethyl carbonate

379 grams of the organic phase stream were brought into contact in a stirred 1 liter reactor with 137.3 grams of ethyl carbonate at a temperature of 10 75°C. The extraction solvent/solution to be separated ratio was 36.2% W/W. After separating by settling at 75°C, the two phases formed were withdrawn and analyzed:

The upper phase, in which the HMTBA was extracted, 15 represented 455.5 g and had a load of salts of 2.4% W/W. Thus, with the participating organic solvent/solution to be treated ratio used, 73.9% of the salts present in the medium before extraction could be displaced into the aqueous phase created by the 20 addition of ethyl carbonate.

The lower phase, into which the salts are partially displaced, represented 60.8 grams and had a load of HMTBA of 2.5% W/W. Thus, under these displacement conditions, 99.4% of the participating 25 HMTBA could be extracted with ethyl carbonate in one

stage with a participating organic solvent/solution to be treated ratio of 36.2% W/W.

The lower phase, for its part, had a load of salts of 50.6% W/W.

5. The partition coefficient, expressed as follows

[salts]lower phase/[salts] upper phase, is 21.1.

6 - Example of extraction of the salts by addition of MEK

379 grams of the organic phase stream were
10 brought into contact in a stirred 1 liter reactor with
137.3 grams of MEK at a temperature of 75°C. The
extraction solvent/solution to be separated ratio was
36.2% W/W. After separating by settling at 75°C, the
two phases formed were withdrawn and analyzed:
15 The upper phase, in which the HMTBA was extracted,
represented 467 g and had a load of salts of 2.1% W/W.
Thus, with the participating organic solvent/solution
to be treated ratio under consideration, 76.5% of the
salts present in the medium before extraction could be
20 displaced into the aqueous phase created by the
addition of MEK.

Sub P ~~The lower phase, into which the salts are partially displaced, represented 49.3 grams and had a load of HMTBA of 2% W/W. Thus, under these displacement conditions, 99.5% of the participating HMTBA could be extracted with ethyl carbonate in one stage with a~~

~~participating organic solvent/solution to be treated ratio of 36.2% w/w.~~

The lower phase, for its part, had a load of salts of 64.8% w/w.

5 The partition coefficient, expressed as follows [salts] lower phase/[salts] upper phase, is 30.9.